The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte SUZANNE DE LA MONTE and JACK R. WANDS

Appeal No. 2006-0275[1]
Application No. 09/964,667

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U.S. PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

HEARD: March 9, 2006

Before SCHEINER, GRIMES and GREEN, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves a method of treating neuroectodermal tumors, malignant astrocytomas, or glioblastomas, by administering an antisense oligonucleotide or a ribozyme complementary to AD7c-NTP, a neural thread protein expressed in neuronal cells and over-expressed in the brains of Alzheimer's disease patients. The examiner has rejected the claims as lacking enablement. We have jurisdiction under 35 U.S.C. § 134. We will affirm this rejection.

[1] This appeal is related to an appeal in application serial no. 09/964,412 (appeal no. 2006-0299). We have considered the two appeals together.

BACKGROUND

AD7c-NTP cDNA was isolated from a cDNA library prepared from the temporal lobe of an individual with end-stage Alzheimer's disease. Specification, page 33. According to appellants, the 1442-nucleotide AD7c-NTP cDNA "is an Alu sequence-containing gene" and "encodes a ~41 kD membrane spanning protein" (id., page 17). AD7c-NTP is expressed in normal brain tissue, but "[q]uantitation of data obtained from 17 AD and 11 age-matched control brains demonstrated significantly higher levels of AD7c-NTP gene expression in AD. In situ hybridization and immunostaining studies localized AD7c-NTP gene expression in neurons, and confirmed the over-expression associated with AD neurodegeneration . . . [These] results suggest that . . . abnormal expression of AD7c-NTP is a phenotype associated with Alzheimer's disease." Id., page 18.

In addition, various neuronal cell lines were stably transfected with AD7c-NTP cDNA and examined for growth properties, morphology, and expression of AD7c-NTP. Specification, pages 45 and 46. "Over-expression of AD7c-NTP . . . resulted in significantly lower densities of viable cells in the cultures, despite normal or elevated levels of DNA synthesis" (id., page 46). The "[r]educed cell density in the cultures was caused by increased cell death" (id.), as shown by the invariable presence of "numerous round, refractile floating [dead] cells" (id.). According to appellants, "[t]he attendant increase in nuclear p53 expression in AD7c-NTP transfected cells suggests that the cell death is likely to be mediated by apoptosis" (id.), i.e., that "over-expression of AD7c-NTP in neuronal cells causes apoptosis" (id., page 9). Finally, viable cells in the AD7c-NTP transfected

cultures exhibited "extensive neuritic growth with fine interconnecting processes [ ] on most cells" and "[i]mmunocytochemical staining . . . using [an] [anti-AD7c-NTP] monoclonal antibody revealed intense labeling of the cell bodies and cell processes" (id.).

According to appellants, "[t]hese studies demonstrate that over expression of AD7c-NTP in transfected neuronal cells promotes neuritic sprouting and cell death, two of the major features of Alzheimer's disease neurodegeneration." Specification, page 46. Thus, reducing AD7c-NTP expression "might be effective in . . . treating or preventing the onset of Alzheimer's disease" (id., page 46).

In addition, the specification teaches that "AD7c-NTP is produced by neuroectodermal tumor cells, malignant astrocytoma cells, [and] glioblastoma cells" (id., page 25). Thus, according to appellants, AD7c-NTP antisense oligonucleotides "may be active in treatment against . . . neuroectodermal tumors, malignant astrocytomas, and glioblastomas" (id.).

DISCUSSION

Claims 35, 37-43 and 45, the only claims remaining in the application, are directed to treating neuroectodermal tumors, malignant astrocytomas, or glioblastomas by administering an antisense oligonucleotide or a ribozyme to inhibit translation of AD7c-NTP mRNA. Claim 35 is representative:

> 35. A method for the treatment of neuroectodermal tumors, malignant astrocytomas, or glioblastomas, said method comprising administering to an animal in need thereof an antisense oligonucleotide which is complementary to an NTP mRNA sequence corresponding to nucleotides 150-1139 of SEQ ID NO:1.

All of the pending claims stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The examiner concedes that "antisense may be used in treatment of disease" (Answer, page 14), but argues that the specification "provides only general guidance for the various antisense based nucleic acid compounds used in the claimed method" (id. page 4), even though "[t]he art of nucleic acid based therapies is [ ] unpredictable" (id., page 6). Moreover, the examiner argues that "the specification has not even shown any particular cancer disease that has as its causation, an overexpression of AD7c-NTP" (id., page 7). Along the same lines, the examiner argues that the specification "does not identify any particular cancer where the inhibition of [AD7c-NTP] activity or expression is ameliorative" (id., page 10).

"When rejecting a claim under the enablement requirement of section 112," it is well settled that "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

"Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.

Cir. 1988).[2] That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis original). In any case, as explained in PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), undue experimentation has little to do with the quantity of experimentation; it is much more a function of the amount of guidance or direction provided:

> [T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

The examiner cites a number of references as evidence of "the unpredictability and the problems faced in the antisense art" (Answer, page 7). The problems or challenges enumerated by the examiner are essentially these: identification of an appropriate target in the disease process; identification of an antisense molecule that can interfere with the disease process through specific recognition and affinity; delivery of antisense oligonucleotides to the brain; the complexity of cellular uptake of antisense oligonucleotides; physical barriers due

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[2] Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (footnote omitted).

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

to internal structures of target RNAs and associations with cellular proteins; and so-called non-antisense effects. Id., pages 6-8.

The examiner concedes that the resolution of these problems involves experimentation of a "more or less standard (albeit empirical and unpredictable) nature" (id., page 12), but argues that the type of experimentation "is outweighed by the sheer quantity of experimentation . . . , the unpredictability of the art generally and the claimed method in particular, and the lack of guidance in the specification regarding the direction in which experimentation should proceed" (id.).

We have no reason to doubt the examiner's assessment of the state of the art in general, and we think it is fair to say that the evidence of record shows that, at the time of the invention, those of skill in the art recognized that considerable experimentation would be needed before antisense therapy would be ready for broad clinical application. Nevertheless, to the extent the examiner focuses on sources of "unpredictability and [ ] problems [ ] in the antisense art" in general (Answer, page 7), rather than the claimed method in particular, we do not agree that that is sufficient to establish that those skilled in the field of antisense therapy would have considered the experimentation required to practice the claimed invention to be undue. What is considered undue is relative – it varies from one field to another. See, e.g., Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (factors relating to undue experimentation include quantity of experimentation necessary, nature of the invention, and relative skill of those in the art).

In our view, the evidence of record establishes that a considerable amount of experimentation and unpredictability was considered to be acceptable in the field of antisense therapy at the time of the invention. Much of the evidence cited by the examiner shows that several clinical trials of antisense drugs had been approved or were ongoing at the time of the invention, despite a widespread recognition in the art that the effects of administering oligonucleotides in vivo were highly variable and complex, and the clinical results generally modest. For example, the examiner cites Jen[3] as evidence of "the challenges that remain before the use of antisense becomes routine in a therapeutic setting" (Answer, page 9), but it is notable that Jen also provides evidence of the approval of "a number of phase I/II trials employing oligonucleotides" (Jen, page 315), despite the fact that "virtually all have been characterized by . . . only modest clinical effects" (id.). Similarly, Agrawal[4] describes several Phase I, II and III clinical trials involving first-generation antisense oligonucleotides (Agrawal, Table 1), while at the same time recognizing the need for "the development of second-generation oligonucleotides, [to] provide improved safety and efficacy" (id., page 386), i.e., to provide improved biological, pharmacokinetic and pharmacodynamic properties (id., page 378, Box 1).

In our view, the approval of multiple clinical trials involving antisense oligonucleotides prior to and at the time of the invention provides evidence that

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[3] Jen et al., "Suppression of Gene Expression by Targeted Disruption of Messenger RNA: Available Options and Current Strategy," Stem Cells, Vol. 18, pp. 307-319 (2000).

[4] Agrawal, "Antisense Oligonucleotides: Towards Clinical Trials," Tibtech, Vol. 14, pp. 376-387 (October 1996).

those of skill in the art would not have considered the general problems cited by the examiner to be a source of undue experimentation in this particular field. Moreover, it is well settled that a therapeutic method need not be ready for broad clinical application in order to be enabled. See In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995): "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development."[5]

That being said, however, we agree with the examiner that the mere observation that AD7c-NTP is expressed at some level in neuroectodermal tumors, malignant astrocytomas, and glioblastomas (Specification, page 25) does not establish a correlation between inhibiting AD7c-NTP and treating neuroectodermal tumors, malignant astrocytomas or glioblastomas (Answer, page 5). That is, we do not agree with appellants' assertion that "the scope of the claims on appeal is commensurate with the teachings of the specification" (Reply Brief, page 1).

According to the specification, AD7c-NTP is produced in neurons in normal brain tissue (Specification, page 18). In addition, "AD7c-NTP is produced by neuroectodermal tumor cells, malignant astrocytoma cells, glioblastoma cells, and in relatively high concentrations (i.e., relative to controls) in brain tissue of [Alzheimer's disease] patients" (id., page 25). The specification teaches that neural cells that over-express AD7c-NTP develop morphological features

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[5] The Brana court wrote in terms of "usefulness," but the rejection on appeal was based on 35 U.S.C. § 112, first paragraph. See 51 F.3d at 1564, 34 USPQ2d at 1439.

characteristic of Alzheimer's disease, and also exhibit increased levels of cell death through apoptosis (id., page 46). The specification does not indicate whether AD7c-NTP is over-expressed in neuroectodermal tumor cells, malignant astrocytoma cells, and glioblastoma cells (all malignant cells of neural origin), or whether the level of expression is comparable to that of normal neurons.

In our view, it is reasonable for the examiner to question whether "any particular cancer disease [ ] has as its causation, an overexpression of AD7c-NTP" (Answer, page 7). Moreover, we note that the specification teaches that that inhibition of AD7c-NTP expression should result in "the reduction of frequency of . . . nerve cell death" (Specification, page 6). That is, inhibition of AD7c-NTP expression should result in a reduction in the frequency of apoptosis, generally considered a desirable process in destroying tumor cells. Thus, in our view, it is reasonable for the examiner to question appellants' "conclu[sion] that interfering with AD7c-NTP expression through the use of antisense oligonucleotides and ribozymes would effectively treat neuroectodermal tumors, malignant astrocytomas and glioblastomas" (Reply Brief, page 4).

We find that the examiner has set forth a reasonable basis for his conclusion that the scope of protection provided by the claims is not adequately enabled by the description of the invention provided in the specification, which appellants have not rebutted by evidence or argument. Accordingly, the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement is affirmed.

TIME PERIOD FOR RESONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Toni R. Scheiner)
Administrative Patent Judge)
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Eric Grimes) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
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